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Hyperthyroidism in pregnancy

Dr. Arosemena does not have any relevant financial relationships with any commercial interests.

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Hyperthyroidism in pregnancy

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Endocrinology fellow
October 2020

Objectives

- Review the differential diagnosis of hyperthyroidism in pregnancy
- Review treatment options and route of administration of ATD during pregnancy
- Review treatment goal of patients with hyperthyroidism during pregnancy

Chief complaint

- 34 y/o G3P2002 pregnant woman (~14 weeks gestation) presents to the ED with intractable nausea and emesis

HPI

- She presented to the ED with generalized malaise, nausea and vomiting throughout the duration of her pregnancy (14 weeks).
- Over the past 2 weeks nausea and emesis worsen and was having about 20 episodes of non-bloody emesis per day. She additionally developed generalized weakness with multiple falls but denied hitting her head or abdomen.
- She reported poor PO intake and 40 lbs weight loss despite pregnancy.
- She had one visit at Mercy with OB/GYN where she had an OB US showing a normal intrauterine embryo.
- 1 ED visit with same complaints but was sent home on ondansetron.
- She denied any palpitations, tremors or hyperdefecation.

- **PMH:**

Thyroid nodule s/p FNA with benign results

- **OB/GYN hx:** 2 children, uncomplicated pregnancies with vaginal delivery.

- **PSH:** Denies

- **FH:** Sister, mother and aunt with goiter. Grandmother with goiter and hyperthyroidism

Additional history

- On further questioning she endorsed periorbital swelling.
- Family members reported increased somnolence
- Prior to pregnancy was feeling at baseline and denied tremors, palpitations.
- Smokes marijuana, denied tobacco or alcohol use.
- **ROS:** +weight loss +nausea + emesis +new rash and +weakness

More history…

- Meds:

Ondansetron PRN

- Allergies: NKDA

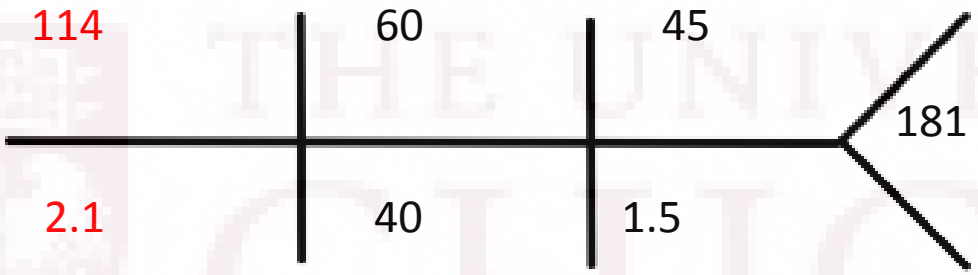
Physical exam

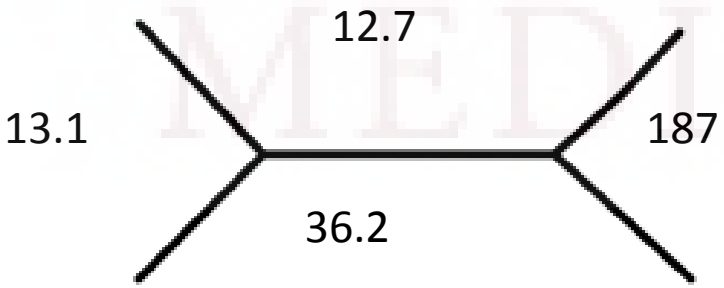
- **Vitals:** BP: 173/75, HR: 112, RR: 19, SpO2: 97%, T: 37.6 °C, Height: 175.3 cm, Weight 90.7kg, BMI: 30.36 kg/m^2

General: somnolent, in mild distress
Skin: macular rash in bilateral upper extremities
HEENT: EOM intact, anicteric, clear sclera. No exophthalmos/proptosis
Neck: firm enlarged thyroid gland, no nodules palpated and +bruit, non tender, no lymphadenopathy.

Cardio: tachycardic, regular rhythm. S1, S2 no murmur/gallop/rub. No S3, S4.
Pulmonary: CTAB. No wheezes/rales/crackles.
Abdomen: soft, non-tender, non-distended.
Extremities: no cyanosis, clubbing or edema.
Neuro: Arousable, following commands. Responding to questions and going back to sleep. Fine tremor+. Reflexes are 2+ throughout.

Admission labs





TSH <0.01
fT4 >7.77
T3 >651
TT4 >24.9

Labs

Ca: 10.3
Mg: 2.6
PO4: 3.1

Total protein: 7.4
Albumin: 4
Total bilirubin: 5.7
Direct bilirubin: 4.2

AST: 463
ALT: 1373
ALP: 134

Lactic acid: 1.5

Random cortisol: 37.6

DAU: +Cannabinoids

Additional Thyroid labs

TPO ab: <0.4

Tg ab: <0.4

Tg: >100

TSI pending

Other imaging studies…

- CXR: No radiographic evidence of acute cardiopulmonary disease. Normal heart size. Lungs within normal limits.
- CT head w/o contrast: No abnormalities
- US abdomen w/doppler: Hepatomegaly, mild coarsening of hepatic echotexture, nonspecific, seen with parenchymal dysfunction. Patent hepatic vascularity. Increased renal parenchymal echogenicity

Hyperthyroidism in pregnancy

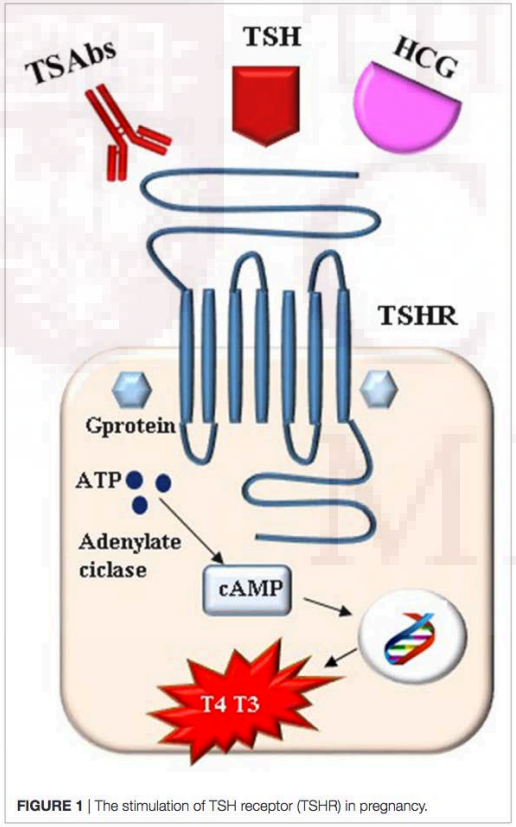
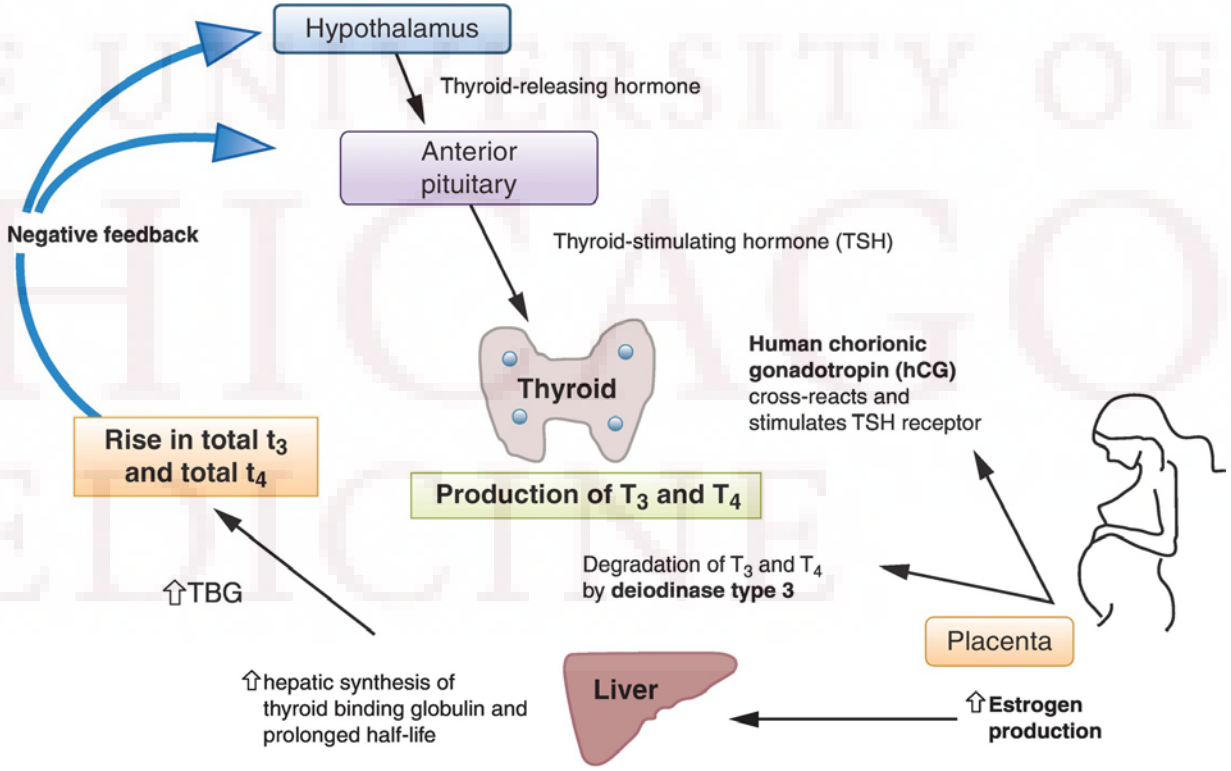


FIGURE 1 | The stimulation of TSH receptor (TSHR) in pregnancy.



Front. Endocrinol., 30 June 2017

Differential diagnosis of hyperthyroidism in pregnancy

- Chorionic gonadotrophin (hCG)-mediated hyperthyroidism or gestational thyrotoxicosis (1% to 3%)
- Graves' disease (0.1% to 1.0%)
- Toxic multinodular goiter
- Toxic adenoma
- Subacute painful or painless thyroiditis
- Excess HCG- Trophoblastic tumors (choriocarcinoma or hydatiform mole)
- Thyrotoxicosis factitial

Hyperthyroidism. Lancet. 2016;388(10047):906-918.
Hyperthyroidism in pregnancy. BMJ Clin Evid. 2015;2015:0611.

Graves' disease vs. Gestational thyrotoxicosis?

Graves' disease	Gestational thyrotoxicosis
Personal or family history of autoimmunity	No personal or family history of autoimmunity
May exhibit overt hyperthyroid features Moderate to severe	May present with hyperemesis, volume depletion, electrolyte imbalance, >5% weight loss Self limited, mild
Diffuse goiter may be present	No goiter
Ophthalmopathy may be present	No ophthalmopathy
TRAb, TPOAb positive	TRAb, TPOAb negative
TT3/TT4 ratio >20	TT3/TT4 ratio <20
HCG normal for gestational age	HCG higher for gestational age
Needs treatment with ATD	T4 returns to normal by 14–18 weeks gestation, no need for ATD

Hyperthyroidism in Pregnancy. Endotext. South Dartmouth (MA): MDText.com, Inc.; February 9, 2019.
Graves' hyperthyroidism in pregnancy. *Curr Opin Endocrinol Diabetes Obes*. 2019;26(5):232-240

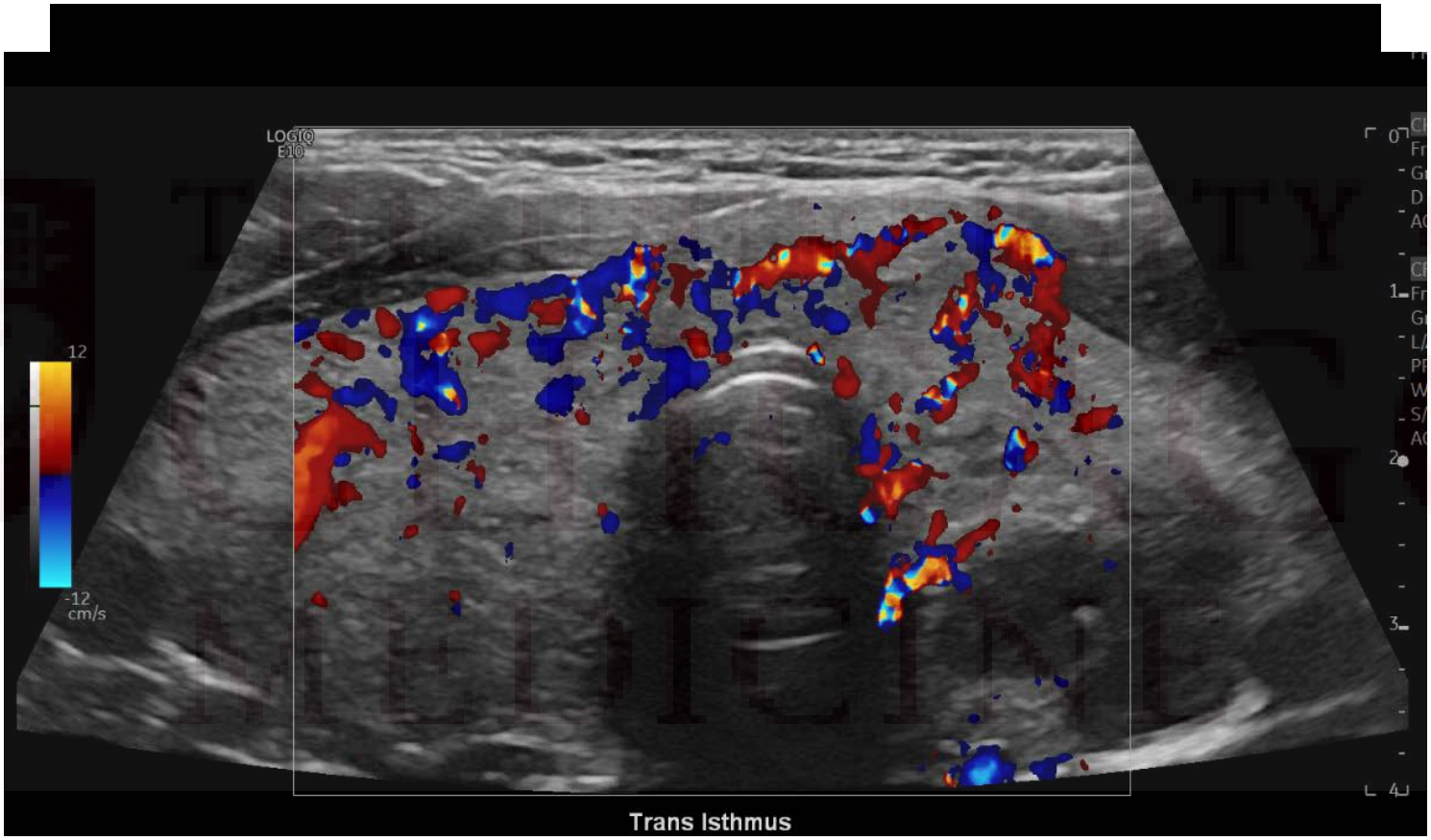
What will you order next?

- TSI
- HCG
- Thyroid Ultrasound

TSI < 1

HCG: 94,1232
[1st trimester pregnancy: 10-200,000]

Thyroid ultrasound



- **Enlarged thyroid gland with increased vascularity, which is seen with thyroiditis.**
- **Dominant lower pole left thyroid nodule, predominantly spongiform, very low morphologic suspicion. The nodule has met size threshold for biopsy (2.7x1.8x2.3cm)**

Will negative TSI rule out Graves' disease?

ORIGINAL ARTICLE

WILEY

Diagnostic testing for Graves' or non-Graves' hyperthyroidism: A comparison of two thyrotropin receptor antibody immunoassays with thyroid scintigraphy and ultrasonography

Lorenzo Scappaticcio[1,2] | Pierpaolo Trimboli[2] | Franco Keller[3] | Mauro Imperiali[3] |

Test	Sensitivity,% (95% CI)	Specificity,% (95% CI)	Accuracy,%	PPV,%	NPV,%
TRAb $_{\text{cut-off 0.7 IU/L}}$ Kryptor®	93 (85.4-97.4)	86.8 (71.9-95.5)	91.1	94	84.6
TSI $_{\text{cut-off 0.1 IU/L}}$ – Immulite®	94.2 (86.9-98.1)	84.2 (68.7-93.9)	91.9	93.1	86.5
US pattern 3	69.8	92.1	76.6	95.2	57.5
TcTU $_{\text{cut-off 1.3\%}}$	95.3 (88.5-98.7)	96.4 (81.6-99.4)	95.6	98.7	87.0

Clin Endocrinol (Oxf). 2020;92(2):169-178.

Endocrine Journal 2015, **62** (6), 557-560

NOTE

Serum human chorionic gonadotropin levels and thyroid hormone levels in gestational transient thyrotoxicosis: Is the serum hCG level useful for differentiating between active Graves' disease and GTT?

Ai Yoshihara, Jaeduk Yoshimura Noh, Koji Mukasa, Miho Suzuki, Hidemi Ohye, Masako Matsumoto, Yo Kunii, Natsuko Watanabe, Nami Suzuki, Toshiaki Kameda, Kiminori Sugino and Koichi Ito

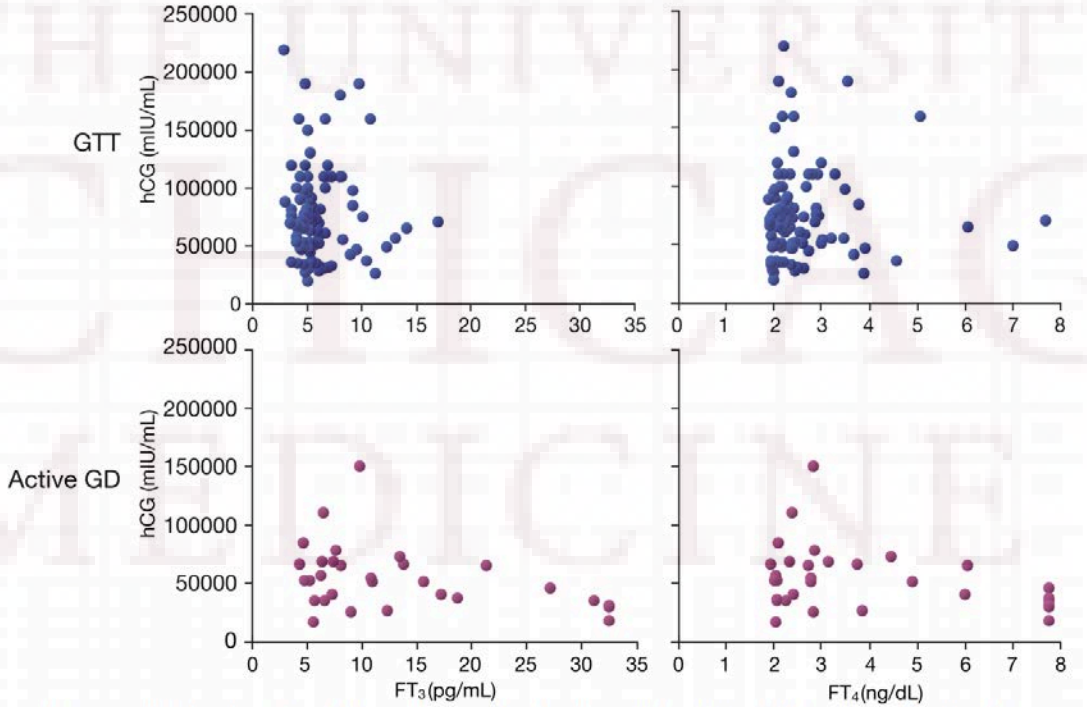


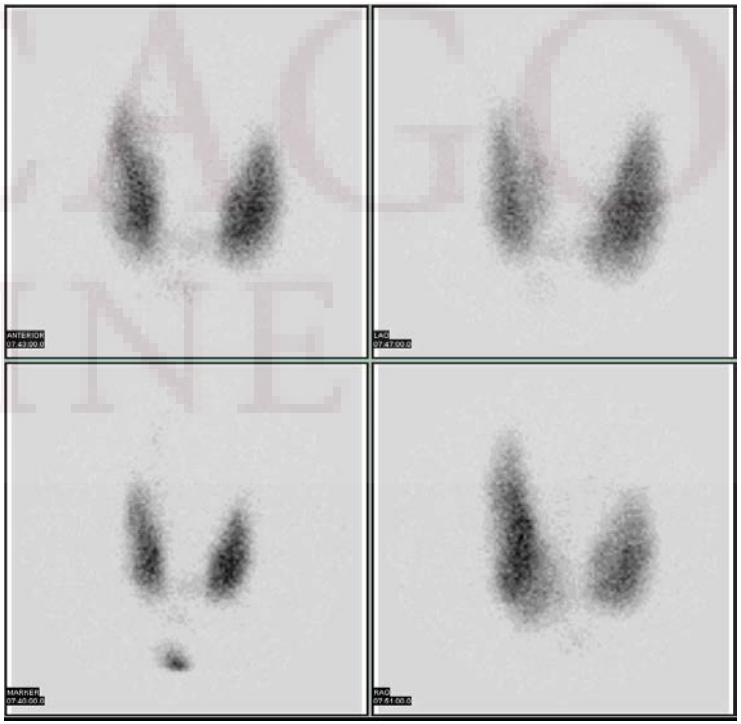
Fig. 1 Serum hCG levels and free thyroid hormone levels (FT_3 or FT_4) in the GTT group and active GD group.

The ROC curve analysis revealed that the cut-off hCG level for differentiating between active GD and GTT was 70,000 mIU/mL.

Endocr J. 2015;62(6):557-60

How will you refine your differential?

- Thyroid biopsy?
- Thyroid uptake and scan?



Treatment

- Will elevated LFTs affect how you treat this patient?
- Thionamides vs. observation?
- Thyroid storm/Severe thyrotoxicosis vs. hyperthyroidism treatment?

Severe thyrotoxicosis

Day 1: -Burch-Wartosfky scale: 45. Patient with confusion and somnolence. Initially started on PO PTU 500 mg loading dose followed by 250 mg q4h, Hydrocortisone 100 mg q8h, Metoprolol tartrate 50 mg q8h. Received IVF for hypovolemic hyponatremia.

Later switched to Propranolol 60 mg q8h switched

TABLE 7. THYROID STORM: DRUGS AND DOSES

Drug	*Dosing*	*Comment*
Propylthiouracil[a]	500–1000 mg load, then 250 mg every 4 hours	Blocks new hormone synthesis Blocks T_4-to-T_3 conversion
Methimazole	60–80 mg/d	Blocks new hormone synthesis
Propranolol	60–80 mg every 4 hours	Consider invasive monitoring in congestive heart failure patients Blocks T_4-to-T_3 conversion in high doses Alternate drug: esmolol infusion
Iodine (saturated solution of potassium iodide)	5 drops (0.25 mL or 250 mg) orally every 6 hours	Do not start until 1 hour after antithyroid drugs Blocks new hormone synthesis Blocks thyroid hormone release Alternative drug: Lugol's solution
Hydrocortisone	300 mg intravenous load, then 100 mg every 8 hours	May block T_4-to-T_3 conversion Prophylaxis against relative adrenal insufficiency Alternative drug: dexamethasone

[a]May be given intravenously.

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

Thyrotoxicosis in pregnancy

PTU is recommended in first trimester
Consider switching to MMI from second trimester
Use lowest effective dose of ATD
Consider reducing dose or stopping ATD in later pregnancy
Monitor treatment with FT4 and TSH: Initially 2-4 weekly, later 4-6 weekly.
Aim for FT4 at or just above the upper end reference range

- Beta-blockers are relatively contraindicated, but not absolutely, propranolol can be used until T4 levels normalized

- The complications of the drugs include:

-Lower Apgar scores
-Intrauterine growth retardation
-Postnatal bradycardia
-Hypothermia and hypoglycemia
-Neonatal respiratory distress

Hyperthyroidism in Pregnancy. Endotext. South Dartmouth (MA): MDText.com, Inc.; February 9, 2019.

Why?

- Methimazole is associated with birth defects including aplasia cutis and choanal or esophageal atresia
- PTU is the preferred medication during the first trimester.
- Consider switching to methimazole after the first trimester because the risk of liver failure associated with PTU use is greater than the risk of congenital abnormalities

Choice and side effects

Clinical Thyroidology / Review

European
Thyroid Journal

Eur Thyroid J 2012;1:176–185
DOI: 10.1159/000342920

Received: July 23, 2012
Accepted after revision: August 23, 2012
Published online: September 24, 2012

Side Effects of Anti-Thyroid Drugs and Their Impact on the Choice of Treatment for Thyrotoxicosis in Pregnancy

Peter N. Taylor[a, b] Bijay Vaidya[c]

[a]Thyroid Research Group, Institute of Experimental and Molecular Medicine, School of Medicine, Cardiff University, Cardiff, [b]London School of Hygiene and Tropical Medicine, London, and [c]Department of Endocrinology, Royal Devon and Exeter Hospital and Peninsula Medical School, Exeter, UK

Eur Thyroid J. 2012;1(3):176-185.

Choice and side effects

Table 1. Case-control and cohort studies of major congenital abnormalities following exposure to ATD in utero

Report	Country	Study type	Agent studied	Key outcomes
Momotani et al. [18]	Japan	Prospective study of 643 neonates divided into 4 groups depending on MMI exposure and maternal thyroid status during the first trimester	MMI	Highest incidence of congenital malformations was in untreated women with hyperthyroidism ($p < 0.01$)
Di Gianantonio et al. [69]	Italy	Prospective study of 241 women counselled by	MMI	No increase in the general rate of major congenital and control, but two dicated choanal as well as e a higher incidence in
Karlsson et al. [33]	Sweden			h oesophageal atresia and sia, 3 of whom had been trimester. No association d PTU
Wing et al. [21]	USA	Retrospective case review of 185 hyperthyroid patients; 99 patients treated with PTU and 36 with MMI	MMI and PTU	No significant difference in congenital abnormalities (2.7% MMI, 3.0% PTU)
Barbero et al. [70]	Argentina	Multi-centre case control (61 cases of choanal atresia, 183 controls)	MMI	Odds ratio for choanal atresia if exposed to MMI = 17.75 (95% CI 3.49–121.40)
Rosenfeld et al. [32]	Israel	Prospective observational controlled cohort study of 115 PTU-exposed pregnancies of women counselled by the Israeli Teratology Information Service; 1,141 controls	PTU	Rate of major anomalies was comparable between the PTU group (1.3%), and control (3.2%), $p = 0.51$
Clementi et al. [30]	Italy	Case-control study of over 18,000 congenital abnormalities; of these, 127 exposed to ATD in the first trimester	CBZ/MMI and PTU	Significant association between exposure to CBZ/MMI and choanal atresia and omphalocele ($p < 0.01$). Potential link between PTU and cardiac defects
Koening et al. [71]	France	Retrospective analysis (Nice Pharmacovigilance Department)	MMI	6 cases of MMI embryopathy, no cases reported with PTU

Major adverse outcomes secondary to CBZ/MMI and PTU are rare, and inadequately treated hyperthyroidism poses a far greater risk

Eur Thyroid J. 2012;1(3):176-185.

Recommendations

Table 4. Society recommendations regarding the use of anti-thyroid drugs in pregnancy

Authorities	Year	Recommendations
American College of Obstetrics and Gynecology [85]	2002	Either PTU or MMI can be used
British Thyroid Association, Association of Clinical Biochemists and British Thyroid Foundation [86]	2006	Patients on CBZ may be switched to PTU in pregnancy
American Thyroid Association and American Association of Clinical Endocrinologists [87]	2011	PTU in the first trimester; switch to MMI after the first trimester
American Thyroid Association [3]	2011	PTU in the first trimester; patients on MMI should switch to PTU if pregnancy confirmed in the first trimester; switch to MMI after the first trimester
The Endocrine Society [66]	2012	PTU should be used first line, if available particularly in the first trimester. If PTU is not tolerated can convert to MMI. As PTU is rarely associated with liver toxicity should change from PTU to MMI after the first trimester, with thyroid function testing 2 weeks after the transfer; also reasonable to monitor liver function tests every 2–4 weeks whilst on PTU

Eur Thyroid J. 2012;1(3):176-185.

What if PO route is not an option?

Due to persistence nausea/emesis, PTU switched to rectal 200 mg q4h

- Rectal formulations of PTU and methimazole can be prepared either as suppositories or retention enemas.
- When the gastrointestinal tract is completely compromised and neither the oral nor the rectal routes are appropriate, thionamides may be prepared for intravenous administration.
- PTU is relatively insoluble at physiologic pH, therefore its preparation and administration are difficult. Intravenous methimazole is available commercially in Europe and can be prepared by dissolving methimazole powder in normal saline.

Chiha M, Samarasinghe S, Kabaker AS. Thyroid storm: an updated review. J Intensive Care Med. 2015;30(3):131-140. doi:10.1177/0885066613498053

Other therapies available?

- Potassium iodine (5 drops q6h)
- Lithium 300 mg q6-8h with frequent monitoring
- Cholestyramine 1-4g BID
- Therapeutic plasma exchange
- Surgery if intolerant to ATD during second trimester

Thyroid storm: an updated review. J Intensive Care Med. 2015;30(3):131-140. doi:10.1177/0885066613498053

Treatment goal

- Maintain maternal TT4/ FT4 values at, or just above the pregnancy-specific upper limit of normal. TT4 1.5x upper limit of non-pregnant range.

- Pregnant women with Graves' disease usually show remission in the third trimester, allowing them to stop taking ATD.

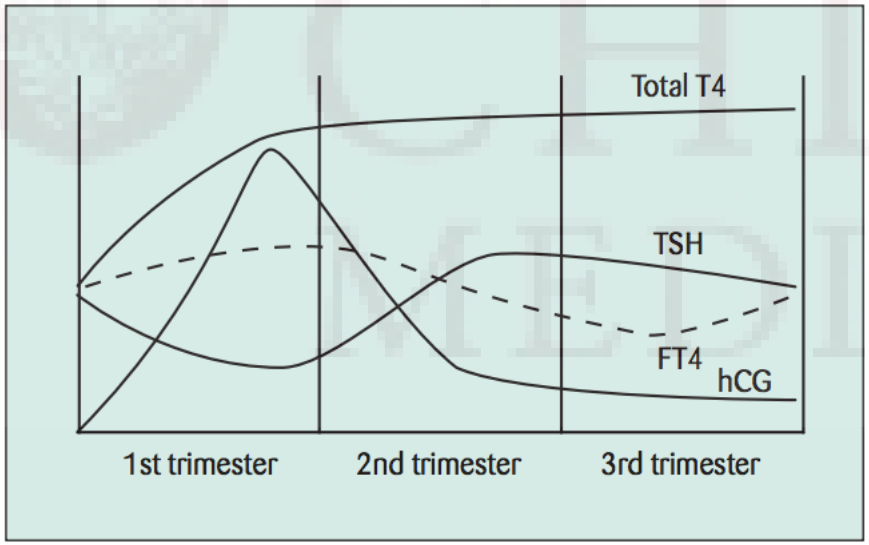


Figure 2. Changes in thyroid hormone levels during normal pregnancy.

Trimester-Specific Reference Ranges for Common Thyroid Tests

TEST	NONPREGNANT	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Thyroid-stimulating hormone (mIU per L)	0.3 to 4.3	0.1 to 2.5	0.2 to 3.0	0.3 to 3.0
Thyroxine-binding globulin (mg per dL)	1.3 to 3.0	1.8 to 3.2	2.8 to 4.0	2.6 to 4.2
Thyroxine, free (ng per dL)	0.8 to 1.7	0.8 to 1.2	0.6 to 1.0	0.5 to 0.8
Thyroxine, total (mcg per dL)	5.4 to 11.7	6.5 to 10.1	7.5 to 10.3	6.3 to 9.7
Triiodothyronine, free (pg per mL)	2.4 to 4.2	4.1 to 4.4	4.0 to 4.2	Not reported

2017 Guidelines of the American Thyroid Associationfor the Diagnosis and Management of Thyroid DiseaseDuring Pregnancy and the Postpartum

Why was the TSI titer negative?

- Pregnancy-induced immunosuppression autoantibodies levels tend to decrease throughout pregnancy.

- The most typical scenario is that the TRAbs are detectable in the first trimester, but levels decrease after 20 weeks of gestation becoming undetectable toward the term of pregnancy. This reflects the amelioration in thyrotoxicosis commonly observed.

Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance. Front Endocrinol (Lausanne). 2017;8:137. Published 2017 Jun 30. doi:10.3389/fendo.2017.00137

Prevalence of Thyrotropin Receptor Germline Mutations and Clinical Courses in 89 Hyperthyroid Patients with Diffuse Goiter and Negative Anti-Thyrotropin Receptor Antibodies

Eijun Nishihara,[1] Shuji Fukata,[2] Akira Hishinuma,[3] Nobuyuki Amino,[1] and Akira Miyauchi[1]

TABLE 2. CLINICAL CHARACTERISTICS OF 11 PATIENTS WITH THYROTROPIN RECEPTOR MUTATIONS

			First visit			*Follow-up*				
Mutation	*Age (years)*	*Sex*	*Goiter (mL)*	*Hyperthyroidism*	*Therapy*	*Period (years)*	*Goiter (mL)*	*Hyperthyroidism*	*Therapy*	*TgAb/TPOAb*
L267F (801G>T)	76	F	35	Overt	None	3	18	Overt	ATD	−/−
L512Q (1535T>A)	20	F	370	Overt	On ATD	10	181	Overt	RI/ATD	−/−
E575K[a] (1723G>A)	61[b]	F	40	Subclinical	None	9	45	Subclinical	None	+/+
	38	M	39	Subclinical	None	5	31	Subclinical	None	−/−
	30	M	36	Subclinical	None	5	37	Subclinical	None	−/−
D617Y[a] (1849G>T)	55	F	11	Subclinical	None	8	18	Subclinical	None	−/−
	48	F	59	Overt	On ATD	8	NT	Overt	Surgery	−/−
	24	F	28	Subclinical	None	8	49	Overt	ATD	−/+
	21	F	22	Overt	None	8	19	Overt	KI	−/−
	20[b]	F	35	Overt	None	8	7.4	Overt	RI	−/−
	20	M	12	Subclinical	None	8	14	Subclinical	None	−/−

[a]Mutation affects several members of the same family.
[b]Proband.
Age, age at diagnosis; F, female; KI, potassium iodide; M, male; RI, radioactive iodine therapy; TgAB, anti-thyroglobulin antibodies; TPOAb, anti-thyroid peroxidase antibodies.

- Prevalence of a TSH receptor mutation - 4.5% in 89 hyperthyroid patients who were unlikely to have Graves' disease or toxic multinodular goiter.
- Juvenile-onset hyperthyroidism who do not have thyroid autoantibodies, including TSAb, TgAb, and TPOAb
- TSH receptor mutations in sporadic cases, typically have a more severe clinical presentation and much stronger activating effect than those in hereditary cases

Thyroid. 2014 May;24(5):789-95

TSH receptor mutation

New variant (Val597Ile) in transmembrane region of the TSH receptor with human chorionic gonadotropin hypersensitivity in familial gestational hyperthyroidism

Philippe Caron[1] | Stéphanie Broussaud[2] | Juan José Galano-Frutos[3,4] | Javier Sancho[3,4,5] | Frédérique Savagner[6,7,8]

Prolonged and Severe Gestational Thyrotoxicosis Due to Enhanced hCG Sensitivity of a Mutant Thyrotropin Receptor

Anne Laure Coulon, Frédérique Savagner, Claire Briet, Marie Vernin, Mathilde Munier, Olivier Chabre, and Patrice Rodien

3 categories:

1. Familial non autoimmune hyperthyroidism (FNAH)
2. Persistent sporadic congenital hyperthyroidism (PSNAH)
3. Gestational thyrotoxicosis with enhanced human chorionic gonadotropin (hCG) sensitivity in the mutant thyrotropin receptor

- Case reports - mutations at the lysine 183 amino acid in the extracellular N-terminal domain of human TSH receptor (hTSHR) have been associated with hypersensitivity to hCG and familial gestational hyperthyroidism

J Clin Endocrinol Metab. 2016 Jan;101(1):10

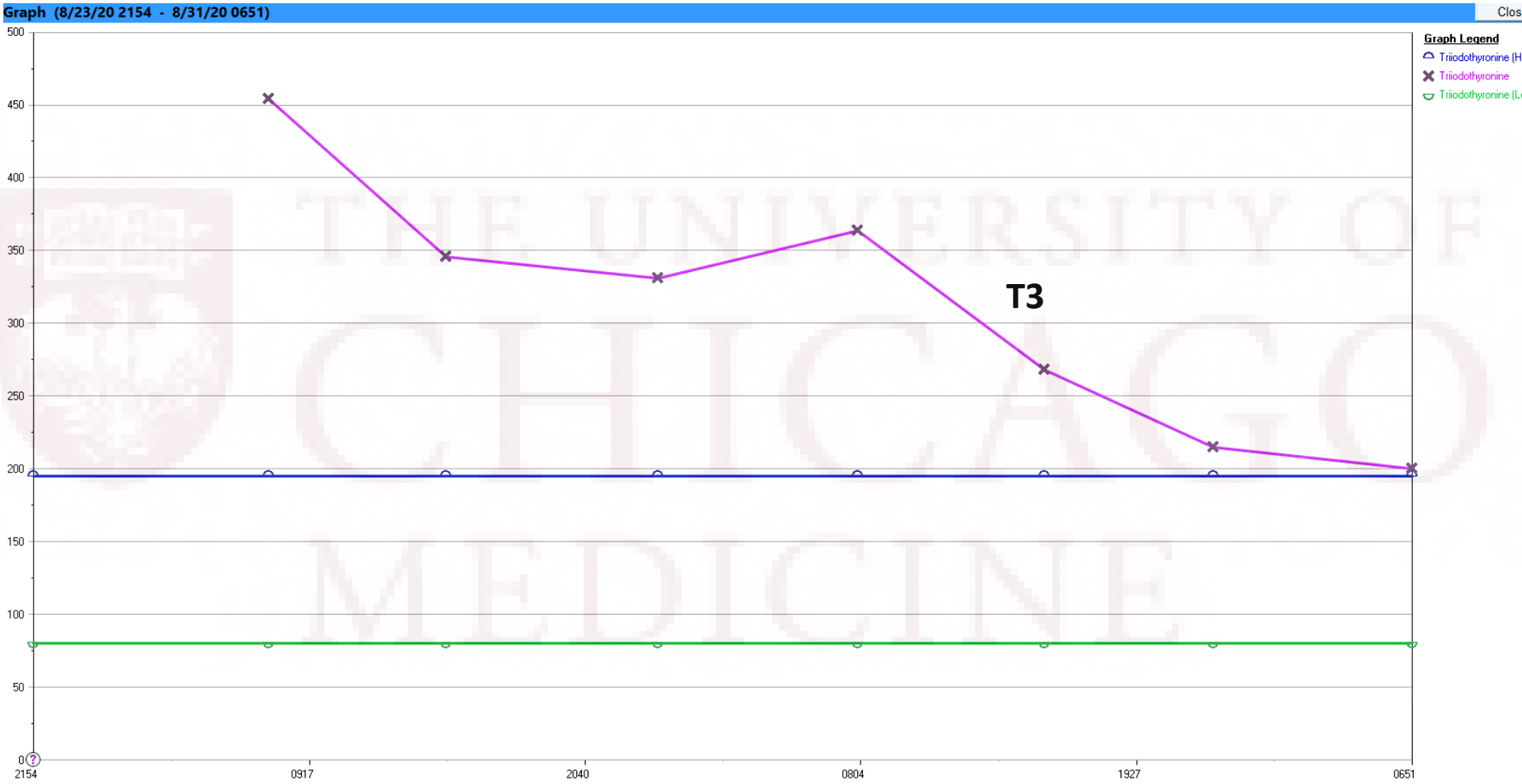
Back to our patient…

Day 2: Somnolence and confusion completely resolved.

Day 3: Swiched PTU to methimazole 30 mg BID. T3 started uptrending again and patient was noted to be agitated.

Day 4: Methimazole increased to 40 mg BID

- Day 7: Mental status back to baseline. Discharged on methimazole 30 mg BID and propranolol 40 mg q8h. Steroids stopped.
- AST and ALT continued to downtrend during hospitalization. By time of discharge AST 151, ALT 632.
- fT4 was 2.49 and T3 200
- Will follow up at Mercy due to insurance issues.


Graph (8/23/20 2154 - 8/31/20 0651)
Clos
Graph Legend
Triiodothyronine (H
Triiodothyronine
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T3
500
450
400
350
300
250
200
150
100
50
0
2154
0917
2040
0804
1927
0651

What about prior labs?

Prior labs
11/2015 TSH 0.30
3/2017 TSH 0.44
2/2019 TSH 0.44
3/2020 TSH 1.24

Conclusion

- During pregnancy hyperthyroidism etiology may be difficult to differentiate but if severe thyrotoxicosis is suspected, treatment should not be delayed.
- HCG-mediated hyperthyroidism is transient, and is frequently (but not always) mild. It generally does not require treatment, but exceptions can occur.
- Graves' disease is suspected when orbitopathy, goiter and TSI are present.
- Be familiar with alternate routes of administration for ATD such as rectal and IV.
- Goal of treatment is to maintain maternal TT4/ FT4 values at, or just above the pregnancy-specific upper limit of normal. TT4 1.5x upper limit of non-pregnant range.